UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,648	10/05/2000	Mark F. Charette	CIBT-P01-569	7787

28120 7590 11/13/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,648	CHARETTE ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-8,16-18,35,37 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5-8,16-18,35,37 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 2, 5-8, 35, 37, and 39-40 have been amended as requested in the amendment filed on August 23, 2006. Applicant has canceled claims 1, 11-12, 19, 22, 25-26, 33-34, 36, and 38 in the August 23, 2006 amendment. Following the amendment, claims 2, 5-8, 16-18, 35, 37, and 39-41 are pending in the instant application.

Claims **2, 5-8, 16-18, 35, 37**, and **39-41** are under examination in the instant action. The claims are examined to the extent of the following elected species: Alzheimer's disease from the disorder group, cytokine antagonist from the agent capable of releasing morphogen activity group, (2-p-bromocynnamylaminoethyl)-5-isoquinolinesulfonamide from the protein kinase A inhibitor group, SEQ ID NO: 2 from the morphogen amino acid sequence group, OP-1 from the morphogen group, and retinoid receptor from the molecule that binds an endogenous ligand group.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn. Any objection or rejection

of record of claims 1, 11-12, 19, 22, 25-26, 33-34, 36, or 38 is rendered moot in view of Applicant's cancellation of said claims.

Withdrawn Objections and/or Rejections

The objection to the specification as set forth at p. 4 of the previous office action mailed 03/23/2006 is withdrawn in view of Applicant's amendment to the specification.

Applicant's arguments, see p. 7 and supporting documents, filed 08/23/2006, with respect to the rejection of claims 2, 5, 8, 35, 37, and 39-41 under U.S.C. 112, second paragraph (as set forth at page 9 of the 03/23/2006 office action), have been fully considered and are persuasive. The rejection of claims 2, 5, 8, 35, 37, and 39-41 has been withdrawn.

The rejection of claims 2, 5-8, 16-18, 35 and 37 under 35 U.S.C. 112, first paragraph (written description), as set forth at page 8 of the previous office action (03/23/2006) is withdrawn in view of applicant's amendments to the claims.

Maintained and New Claim Rejections, Necessitated by Amendment

Claim Objections

The objection to claims 8 and 16-17 as noted at page 4 of the previous office action mailed 03/23/2006 regarding the issue that the claims are not limited to the elected species is maintained and held in abeyance until allowable subject matter is

identified. This objection is also applied to amended claims 2 and 39-41, for also not being limited to the elected species.

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 5, as amended, recites the limitation "wherein said morphogen activity is endogenous". Claim 5 depends from claim 2, which recites the limitation of "endogenous morphogen[s] [effects] *in vitro*". Accordingly, claim 5 fails to further limit claim 2.

Claim Rejections - 35 USC § 112, 1st Paragraph

The rejection of claims 2, 5-8,16-18, 35, 37 and 39 under 35 U.S.C. 112, first paragraph (scope), is maintained for reasons of record, and is further applied to claims 40 and 41, as amended. The specification, while being enabling for a method of reducing leukemia inhibitory factor (LIF)-induced dendritic retraction comprising adding an antibody against gp130 to sympathetic neurons *in vitro* that have been treated with LIF and osteogenic protein-1 (OP-1) and wherein said antibody reduces LIF-induced dendritic retraction, *does not* reasonably provide enablement for a method for promoting neuronal cell growth *in vitro or in vivo*. Additionally, the specification is enabling for a method of reducing ciliary neurotrophic factor (CNTF)-induced dendritic retraction comprising adding phosphatidylinositol-specific phospholipase C (PI-PLC) to

sympathetic neurons *in vitro* before the neurons have been treated with CNTF and OP-1 and wherein said PI-PLC reduces CNTF-induced dendritic retraction. The specification is also enabling for a method of reducing the inhibitory effects of LIF on OP-1 stimulated dendritic growth comprising adding an anti-LIF antibody to sympathetic neurons *in vitro* that have been treated with LIF and OP-1 and wherein said antibody reduces the inhibition of LIF on OP-1 stimulated dendritic growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants assert on page 6 of the response filed August 23, 2006 that the claims have been amended to more precisely describe the subject matter of the invention, and in particular the claims now recite dendritic growth rather than cell growth in general.

Applicant's arguments as they pertain to the rejection have been fully considered but are not found to be persuasive. Contrary to Applicant's assertion that the claims more particularly describe the invention, the amended limitations of, for example, claims 2 and 39 do not negate the previous office action's assertion that the specification is lacking on guidance to enable the artisan to understand and carry out the invention in its full scope. It is noted that the claims still read upon *in vivo* methods of reducing inhibition of a morphogen activity in a neuron or for promoting neuronal cell growth. The limitation "which component reduces inhibition of growth-promoting effects of endogenous morphogens *in vitro*" is an inherent property of the agent being applied, and does not limit the "method for promoting neuronal cell growth" to *in vitro* methods.

In particular, a broad, reasonable interpretation of claim 8, as derived from claim 2 for example, encompasses treatment of such neurodegenerative disorders as Alzheimer's disease, Parkinson's disease, Huntington's disease, and dementia, among others, which have proven to be recalcitrant to treatment in the art (see references listed on p. 13, section (v) of the 07/24/2004 office action). The art recognizes that these diseases are neurodegenerative and result in a loss of neurons due to neuronal death. Thus, neurons injured by such conditions would include dead and dying neurons. It is unclear how such dead or dying neurons could be induced to grow dendrites.

Additionally, the neuronal cell type affected by the method of claims 2, 5-8, 16-18, 35, and 39-41 is not limited to sympathetic neurons nor to neurons in culture (as in claims 2, 5-8, 16-18, and 35). Regarding the instant invention, one skilled in the art would not predict that the *in vitro* results in sympathetic neuronal cell cultures, which have been cultured under conditions to exclude glial and other non-neuronal cells (see p. 29), are predictive of non-sympathetic neurons or neurons *in vivo*, particularly neurons injured by a neurodegenerative condition. Neurons in vivo would be part of an intricate system of neuronal and non-neuronal cells and would be exposed to and influenced by the extracellular environment, which is quite different from *in vitro* culture conditions. Sympathetic neurons, as used in the instant application, are derived from the peripheral nervous system (PNS) and are distinct from neurons derived from the central nervous system (CNS) in terms of responding to environmental stimuli, such as trophic factors, and being influenced by non-neuronal cells. For example, Burnham et al. (*Dev Biol.* 1994; 161(1):96-106) note that the survival of sympathetic neurons (from

the superior cervical ganglion (SCG)) was greater in nerve growth factor (NGF)-supported non-neuron-depleted cultures than in CNTF-supported cultures. However, the sympathetic neurons responded better to CNTF when non-neuronal cells were added to the cultures. In contrast, the majority of neurons in spinal cord neuronal cultures, which are CNS neurons, were found to be dependent on CNTF for survival, and their survival was unaffected by NGF (see Magal et al., *Brain Res Dev Brain Res.* 1991; 63(1-2): 141-150). Further, Nonaka et al. (*Cell Tissue Res.* 1996; 273(3):525-531) report that when catecholaminergic central (locus coeruleus) and peripheral (sympathetic) neurons are compared as to their ability to innervate central (cortex) or peripheral (pineal gland) targets *in vitro*, CNS neuron neurite extension to the targets was only possible in the presence of glial cells, whereas sympathetic neurons extended neurites regardless of the existence of glial or non-glial cells. In summary, the state of the art recognizes that: 1) sympathetic neurons behave differently than neurons of the CNS, and 2) the presence of non-neuronal cells can influence distinct behaviors in either peripheral or central neurons, such that *in vitro* culturing conditions are not predictive of the *in vivo* environment to which neurons are exposed. Undue experimentation would thus be required of the skilled artisan to promote neuronal cell growth in non-sympathetic neurons or to reduce dendritic retraction in non-sympathetic neurons, particularly those neurons injured by neurodegenerative conditions (which primarily and substantially affect the CNS), and especially if the method involves *in vivo* administration of the composition to a subject having said injured neurons.

Applicant has provided little or no guidance beyond *in vitro* data that would enable one of ordinary skill in the art to determine, without undue experimentation, optimal parameters for *in vivo* therapy such as dosages, timing, and methods of administration. What is provided is thus the idea for an invention, and the invitation to experiment to implement this invention, not the invention itself. Applicants' rebuttal in the response filed December 27, 2005 asserts that the dosage and timing of administration of a pharmaceutical composition (i.e., for *in vivo* therapy) must always be individually determined and therefore routine in the practice of the relevant art, and submit the Benet et al. reference (Exhibit C of the December 27, 2005 response) for support of this argument. However, this argument is not found to be persuasive. Even Benet et al. notes that "to use the data that are presented, one must understand clearance concepts and their application for the computation of drug-dosage regimens. One must also know average values of clearance, as well as some measures of the extent and kinetics of drug absorption and distribution." Accordingly, because such values are not provided by the instant application, undue experimentation would be required of the skilled artisan to first determine these values in order *then* determine optimal dosages, timing and methods of administration and to thus practice the invention as recited in the claims.

The specification is enabling for methods of reducing dendritic retraction *in vitro* (or conversely for reducing inhibition of dendritic growth *in vitro*), however, no guidance is provided for methods resulting in neuronal proliferation, growth, and maintenance in the differentiated state. While the instant disclosure provides guidance for *in vitro*

methods of reducing dendritic retraction, dendritic growth does not equate to neuronal proliferation, growth, and maintenance. For example, Bruckenstein and Higgins (*Developmental Biology*, 1988, 128(2): 337-348, as referenced in the previous office action) report that serum-derived factors which affected dendritic sprouting in sympathetic neurons in culture had little effect on axonal outgrowth or neuron proliferation. Accordingly, the art recognizes that induction of neuronal dendritic growth is not predictive of overall neuronal growth, proliferation, or survival.

While claims 39-41 are drawn to *in vitro* methods, the claims as amended recite culture conditions incapable of achieving the desired result, namely, dendritic growth. Claims 39-41 are drawn to methods comprising contacting a neuron with a composition comprising a component, wherein the component is selected from: a monoclonal antibody to a gp130 protein, phosphatidylinositol-specific phospholipase C (PI-PLC) (as in claims 39-41), or additionally selected from (2-p-bromocynnamylaminoethyl)-5-isoquinolinesulfonamide (H-89), and enantiomers of cAMP or dibutyryl cAMP (as in claims 39 and 2). As written, the exposure of one of these components alone to sympathetic neurons would not induce dendritic growth nor reduce dendritic retraction, as evidenced by Figures 5, 9 and Table III on p. 33 of the instant application. These components are shown only to reduce the effects of exogenously applied neuropoietic cytokines, such as CNTF or LIF, and do not affect dendritic outgrowth either when applied to cultured neurons alone or in combination with a morphogen such as OP-1. Additionally, the agent PI-PLC was shown only to antagonize CNTF-specific inhibition of OP-1, and was incapable of affecting LIF-mediated OP-1 inhibition (see Figure 9). A

method requiring PI-PLC would thus be further limited in scope than a method requiring a monoclonal antibody to a gp130 protein, for instance. Because the claims as written do not require a neuropoietic cytokine such as CNTF or LIF to be present in the culture conditions, and the skilled artisan would not expect these or other neuropoietic cytokines to be present in uninjured or unstimulated pure neuronal cultures, undue experimentation would be required to practice the methods of claims 2 and 39-41. For example, the recited methods would require a determination of what exactly is inhibiting the morphogen prior to being able to determine which component would be best suited to overcome this inhibition, because, as previously indicated, not all components will antagonize all morphogen inhibitors.

And upon further examination, the specification provides no guidance or support demonstrating the use of protein kinase A inhibitors, such as H-89 and sterically constrained enantiomers of cAMP and dibutyryl cAMP, to reduce the cAMP-induced inhibition of dendritic growth-promoting effects of morphogens such as OP-1. The instant specification only demonstrates that agents that increase cAMP levels, such as forskolin and dibutyryl cAMP, were capable of reducing OP-1-mediated dendritic growth in a dose-dependent manner. However, there is no indication that the converse would be true, that is, that cAMP inhibitors (or PKA inhibitors, which would interfere with cAMP signaling) would enhance OP-1 dendritic growth. Further, Applicant provides no guidance as to the ability of PKA inhibitors to antagonize CNTF or LIF, which neuropoietic cytokines are responsible for inhibiting OP-1-mediated dendritic growth. As written, the exposure of one of these components alone to neurons would not be

expected to induce dendritic growth nor reduce dendritic retraction, as evidenced by Chijiwa et al. (*J Biol Chem.* 1990; 265(9): 5267-5272). Chijiwa et al. demonstrate that addition of the protein kinase A inhibitor H-89 (which is (2-p-bromocynnamylaminoethyl)-5-isoquinolinesulfonamide of instant claims 2 and 39) to neuronal cultures comprising either forskolin or NGF had no effect on neurite outgrowth, and even *decreased* neurite outgrowth in forskolin-treated neurons (see Figure 4, p. 5269). The art thus recognizes that protein kinase A inhibitors are not sufficient on their own to facilitate growth-promoting effects to a neurons' morphology. Accordingly, one skilled in the art would not expect that such components would be capable of reducing inhibition of dendritic growth-promoting effects of endogenous morphogens, particularly if the inhibition is due to neuropoietic cytokines such as CNTF or LIF.

Therefore, due to the large quantity of experimentation necessary to practice *in vivo* methods and particular *in vitro* methods, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administering a molecule to a subject, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 2nd Paragraph

Claims 5-6, 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "morphogen activity" in claims 39 and 40, and in claims 5-6 as they depend from claims 39 and 40, is a relative term which renders the claims indefinite. The term "morphogen activity" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "morphogen activity" means for example, inducing the migration, proliferation and differentiation of progenitor cells, or stimulating the proliferation, growth, or maintenance of differentiated cells. It is not clear from the specification or the claims which activities are encompassed by this term. As it is inappropriate to read limitations in the specification into the claims, the claims must independently define the invention for which patent protection is sought.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
November 2, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER